



Original Article

Outcome and Toxicity Patterns in Children and Adolescents with Non-Hodgkin Lymphoma: A Single Institution Experience

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Abstract. Background: The incidence and biology of non-Hodgkin lymphoma (NHL) vary according to age. Some data suggest that the impact of age in pediatric and adolescent NHL patients depends on the histological subtype. **Objectives:** We aimed to analyze the impact of age at diagnosis on clinical characteristics and treatment-related toxicity in children and adolescents with NHL.

Methods: Retrospective review of medical records of children and adolescents diagnosed with NHL at the Hospital for Sick Children, Toronto, between January 1995 and December 2008.

Results: 164 children were diagnosed with NHL during the study period, with a median age at diagnosis of 10 years. With a median follow-up of 6.2 years, 5-year OS in patients aged <15 and 15-18 years was 89±2% vs 82%±6%, respectively ($P = 0.30$), and 5-year EFS was 84%±3% vs. 77%±7% ($P = 0.37$). In Burkitt's lymphoma (BL) and lymphoblastic lymphoma (LL) there was a trend towards better outcomes in children compared to adolescents, with EFS of 91%±4% vs. 75%±15%, respectively in BL ($P = 0.17$), and 82%±7% vs. 51.4%±2% respectively in LL ($P = 0.16$). Late effects occurred in 21 patients (12.8%).

Conclusions: Children with NHL aged < 15 years tend to have better survival rates and similar long-term toxicity than adolescents aged 15-18 years.

Keywords: Lymphoma, Age, Adolescents, Toxicity, Outcomes.

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Introduction. Non-Hodgkin lymphoma (NHL) represents approximately 7% of all malignancies in children. The overall incidence of NHL increases with age, and the outcome differs amongst children being marginally less favourable in infants and adolescents.^{1,2} Over the last three decades, significant improvements have been achieved in the outcome of pediatric NHL with

current survival rates ranging between 80 to over 90% in mature B-cell lymphomas,³ and only slightly lower in lymphoblastic lymphomas (LL)⁴ and anaplastic large cell lymphomas (ALCL).⁵ This is mostly due to treatment assignment on the basis of the histological subtype, cytogenetic abnormalities, and disease stage.⁶ Adolescents have been reported to have a poorer outcome

compared to children,⁶ particularly in some histological subtypes such as Burkitt's lymphoma (BL).⁷ This survival difference remains only partially explained and the age cut-off itself, between children and adolescents, has been set at either 14 or 15 years in different studies.⁷ The aim of this retrospective study was to analyze the clinical characteristics and outcome of children with NHL treated at the Hospital for Sick Children in Toronto, Canada, and to determine whether children < 15 years of age have different clinical features, and/or outcomes than adolescents (age 15-18 years). The Hospital for Sick Children is a pediatric tertiary care center, therefore we provided all patients, including the teenagers, consistent care with pediatric protocols, and maximum enrollment into clinical trials when available, thus eliminating some of the issues which have been associated with poor outcomes in adolescents (treatment in adult centers, poor compliance, poor enrolment into clinical trials).

Materials and Methods. Research ethics approval was obtained from our institutional board. Medical records of children \leq 18 years of age with newly diagnosed NHL admitted to the Hospital for Sick Children from January 1995 to December 2008 were retrospectively reviewed. Patients with human immunodeficiency virus infection, congenital immunodeficiency, previous organ transplantation, previous malignancy, previous chemotherapy or radiotherapy and those with a diagnosis of mycosis fungoides were excluded. NHL subtypes were classified according to 2001 WHO Classification of Haematological Malignancies.⁸ Disease staging was performed according to the St. Jude staging system including a physical examination, peripheral blood and bone marrow smears, cerebrospinal fluid (CSF) analyses, serum lactate dehydrogenase (LDH) levels and adequate imaging techniques.⁹ Patients with LL and \geq 25% bone marrow (BM) blasts were diagnosed as acute lymphoblastic leukemia (ALL) and were excluded. Central nervous system (CNS) was considered positive at diagnosis if there were \geq 5 lymphoma cells/ μ l in the CSF and/or cranial nerve palsy and/or cerebral lesions on neuroimaging. Lactate dehydrogenase (LDH) level was considered elevated if it was greater than twice the upper normal limit. B symptoms were defined as fever, drenching night sweats during the last six months, and weight loss at > 10% of

baseline weight. Toxicity was graded as per CTCAE v4.

Therapy. Patients with T and B-cell LL received an ALL-type protocol consisting of a 4-drug induction (prednisone, vincristine, daunorubicin, asparaginase plus intrathecal methotrexate) therapy and consolidation (6-mercaptopurine, cyclophosphamide, cytarabine, prednisone and intrathecal methotrexate) therapy, followed by interim maintenance (high-dose methotrexate and intrathecal methotrexate), delayed intensification (dexamethasone, vincristine, doxorubicin, asparaginase, cyclophosphamide, cytarabine, thioguanine and intrathecal methotrexate) and maintenance therapy (oral 6-mercaptopurine and methotrexate plus monthly pulses of prednisone and vincristine) for a total therapy duration of 24 months. Patients with early-stage NHL including BL, diffuse large B-cell lymphoma (DLBCL), and ALCL were treated with the old POG9219 protocol consisting of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) therapy plus intrathecal methotrexate for two months. When the studies were open to accrual, patients with advanced stage LL, mature B-NHL and ALCL were recruited to the COG protocols A5971, ANHL01P1 and ANHL 0131 respectively. Off study patients received the standard arm of the protocols.

Patients with advanced-stage BL and DLBCL received LMB-96¹⁰ type regimens consisting of a reductive phase (cyclophosphamide, vincristine, prednisone and intrathecal methotrexate and hydrocortisone) followed by induction (vincristine, prednisone, cyclophosphamide, high-dose methotrexate with folinic acid rescue and intrathecal methotrexate and hydrocortisone) therapy and consolidation (high-dose methotrexate with folinic acid, intrathecal methotrexate, hydrocortisone and cytarabine for stage III patients); stage IV patients received a higher dose of methotrexate (8 grams/m²) in induction, high-dose cytarabine and etoposide in consolidation and four cycles of maintenance therapy. Patients with advanced ALCL received the APO regimen consisting of induction (doxorubicin, vincristine, prednisone and intrathecal methotrexate) therapy followed by consolidation (6-mercaptopurine, prednisone, vincristine, doxorubicin until a cumulative dose of 300 mg/m² which was later substituted by intravenous methotrexate) therapy

for 15 cycles. In addition, cranial radiotherapy (CRT) was given to LL and ALCL patients with initial CNS involvement.

Follow up for toxicity monitoring, and disease surveillance was performed according to protocol specific or local standard of care guidelines.

Statistical analyses. Descriptive statistics were reported as absolute frequencies and percentages for qualitative data, while means, standard deviations (SD) and medians were used to describe quantitative variables. Continuous variables were stratified into categorical variables using appropriate criteria. Differences in the frequencies of each variable were evaluated by the chi-squared test and 95% confidence intervals (95% CI) for categorical variables. Overall survival (OS) and event-free survival (EFS) were estimated by the Kaplan–Meier method and the differences were tested using the Log-rank test. EFS was calculated from the date of diagnosis until the first event (death from any cause, disease progression, relapse, or second malignancy) or until the date of the last follow-up. OS was calculated as the percentage of patients who were still alive at last follow-up date. Time was censored at last follow-up date if no failure occurred or if patient was lost to follow-up after completing therapy. Follow-up was updated until June 2013. A formal cumulative incidence analysis was performed regarding toxic deaths versus death related to relapse or progression. Statistical calculations were performed using SPSS software version 20.0 for Windows operating system (SPSS, Cary, NC, USA).

Results.

Patients' characteristics. From January 1995 to December 2008, a total of 164 immunocompetent children \leq 18 years of age were diagnosed with NHL in our Institution. The median age at diagnosis was ten years (range, 1-17) (**Table 1**).

Patients were stratified according to their age at diagnosis into two groups: $<$ 15 (children) and 15-18 years of age (adolescents). The male to female ratio was 1.5:1, with no significant difference between the age groups. The most frequent site of involvement was head and neck in the $<$ 15 year-group and abdomen in the 15-18 year-group. Among all NHL patients, 76% presented with advanced-stage disease (stage III or IV), 15% with elevated LDH, 38% with B symptoms, 11% with BM involvement and 9% with CNS involvement, with no significant differences between the two age groups. BL was diagnosed in 52 patients (33%), ALCL in 48 patients (29%) (including 1 primary CNS lymphoma), LL in 43 patients (26%) and DLBCL in 15 patients (8%) (including 1 primary CNS lymphoma, and 2 primary mediastinal B-cell lymphomas) and peripheral T-cell lymphoma (PTCL) in 6 patients (4%). BL was the most frequent histological subtype among children, while ALCL was the commonest among adolescents. Among 48 patients with ALCL and available Alk-1 reactivity data, 87%, and 77% of children and adolescents were positive, respectively (*Not Significant, NS*). As expected, 88% of LL patients had a T- and 12% had B-precursor immunophenotype.

Treatment outcome. At a median follow-up of 6.2 years (range 0.1–15.7 years), the 5-year EFS for all patients was $82\% \pm 3\%$ and the 5-year OS $88\% \pm 2\%$. EFS was comparable in children $<$ 15 years of age and adolescents ($84\% \pm 3\%$ vs. $77\% \pm 7\%$, $P = 0.37$), as well as 5-year OS ($89\% \pm 2\%$ vs $82\% \pm 6\%$, $P = 0.30$) (**Figure 1A**). When the patients were stratified by histological subtype, some trends became evident. Among BL patients, the 5-year EFS tended to be superior in children compared to adolescents ($91\% \pm 4\%$ vs $75\% \pm 15\%$, respectively; $P = 0.17$). Similarly, children with LL had better EFS than adolescents ($82\% \pm 7\%$ vs $51.4\% \pm 2\%$, $P = 0.16$) (**Figure 1A**).

Table 1. Characteristics of the Patients.

	N	Sex ratio	Age years (median, range)	LDH $>$ 2 x ULN	Stage (%)		Site involvement (%)									EFS (%)	OS (%)
					I/II	III/IV	H/N	P/N	Mediast	Lung	Abd	Bone	Skin	BM	CNS		
BL	52	3.3:1	8.5 (1-16)	27	38	62	54	19	17	10	63	17	0	10	10	88.5 ± 4	90.4 ± 4
DLBCL	15	0.9:1	11 (1-17)	7	33	67	20	27	20	13	40	20	0	7	13	86.7 ± 8	93.3 ± 6
PTCL	6	5:1	11 (4 -16)	50	17	83	33	17	17	17	50	17	17	33	17	50 ± 20	83.3 ± 15
LL	43	1.6:1	7 (2 -17)	19	7	93	72	19	81	2	44	5	0	12	9	77.4 ± 6	84 ± 6
ALCL	48	0.8:1	12 (2 -16)	0	23	77	54	44	35	19	42	25	15	10	8	82.3 ± 5	87.3 ± 5

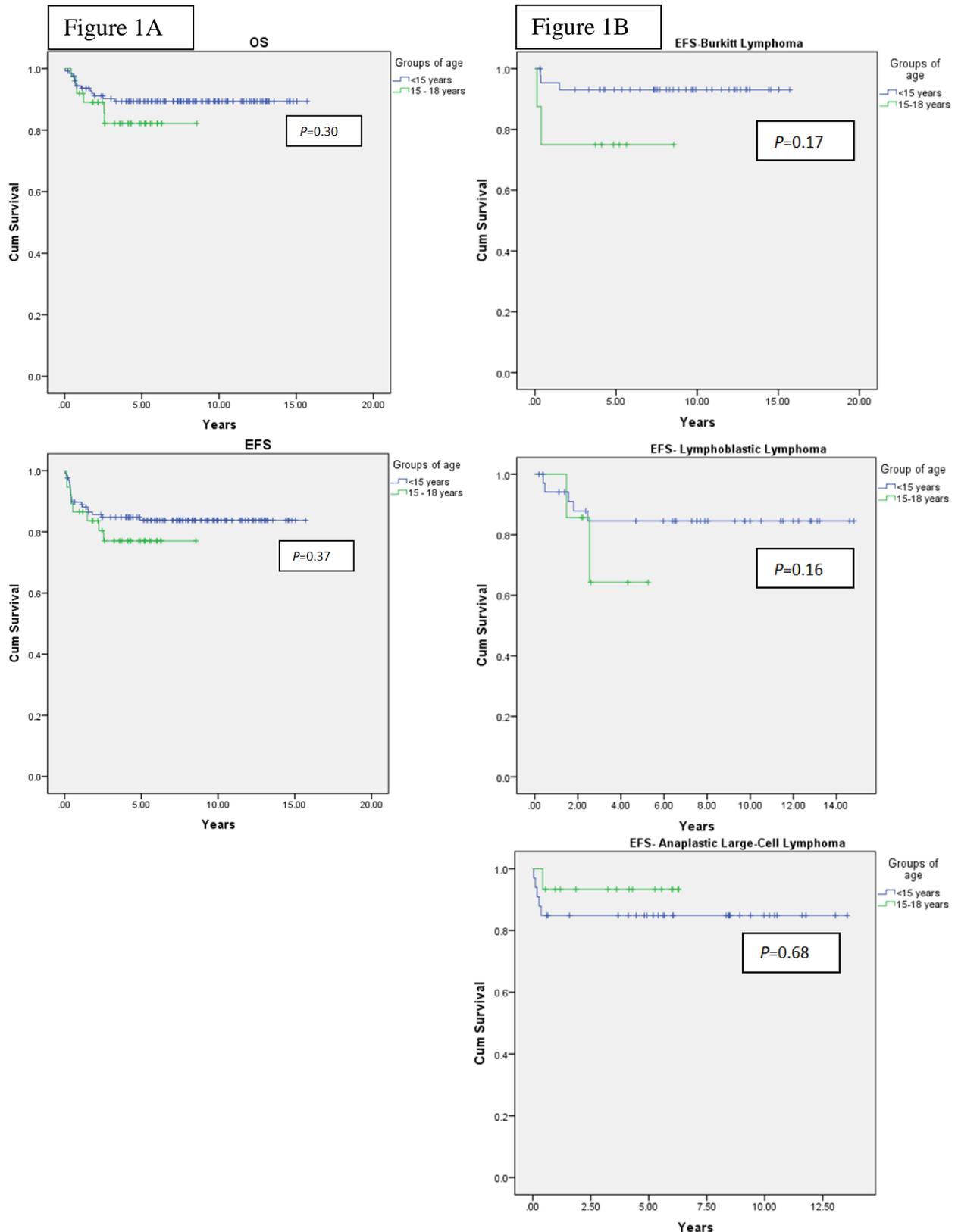


Figure 1A. OS and EFS by age. **Figure 1B.** EFS by age and histological subtype.

Among ALCL patients 5-year EFS was comparable in children and adolescents ($81.4 \pm 7.6\%$ and $87 \pm 7\%$ respectively, $P=0.68$) (**Figure 1B**), irrespective of skin, mediastinum, lung, liver and spleen involvement. Among 6 PTCL patients, 5 children aged < 15 years are currently alive and

disease free and the only adolescent died from treatment-related toxicity.

Overall, twenty patients (12.2%) relapsed, 7 in the primary site only (35%), 4 in CNS alone (20%), 3 in the bone marrow alone (15%), 1 in each of liver only, neck only and testicular only

(5% each site), and 3 (15%) in multiple sites. Five patients with BL (9.6%) relapsed (median time since diagnosis 4 months), as well as 2 (13%) with DLBCL (median time since diagnosis 13.6 months), 8 (19 %) with LL (median time since diagnosis 18.4 months), 3 (6%) with ALCL (median time since diagnosis 6.5 months) and two (33%) with PTCL (median time since diagnosis 5 months). Due to the low number of events, no comparison was possible between children and adolescents. Two patients underwent allogeneic hematopoietic stem cell transplant (HSCT) after one and two salvage chemotherapy regimen(s), and 3 underwent autologous HSCT after one salvage chemotherapy regimen. Twelve patients died from disease progression (7.3%). The cumulative incidence (CI) of death due to disease progression was 7.3% and 9.3% in the patients <15 and 15–18 years, respectively. Six patients (3.7%) died from treatment-related toxicity. The CI of toxic death was 3.6% and 5.7% in the patients aged < 15 and 15–18 years respectively.

Late effects. Twenty-one patients (12.8%) developed late effects related to disease and/or treatment, with no significant differences between children and adolescents (**Table 2**). Patients who had undergone radiotherapy or HSCT (either autologous or allogeneic) were more likely to develop late effects. Six of 17 patients (35.3%) who had received radiotherapy developed late effects, versus 15 of 147 who did not ($P < 0.05$).

One had total body irradiation as part of HSCT conditioning regimen; five had cranial irradiation (4 as upfront treatment due to CNS involvement at diagnosis, one patient due to CNS relapse). Five of 11 patients (45.5%) who underwent HSCT

developed late sequelae, versus 16 of 153 who did not ($P < 0.05$). Two BL survivors developed a second malignancy, a papillary thyroid carcinoma and a myelodysplastic syndrome, both among children <15 years of age, at 6 and 7 years since the end of treatment, respectively.

Discussion. Non-Hodgkin lymphoma is one of the most common cancers diagnosed among adolescents.¹¹ Age has been shown to be of prognostic value in some histology subtypes, but the age threshold is not defined and varies in different histology subtypes. We chose to use 15 years of age as limit between children and adolescents, in line with SEER and ASH definition.¹²

Overall, the demographic characteristics of our patients do not deviate from the literature. Of note, ALCL was the second most common lymphoma and constitutes 29% of the cases in our series, higher than most of the literature data.^{7,13-15} A possible explanation of these differences could be the racial diversity of our Canadian population. Further epidemiological studies on the incidence of lymphoma subtypes in populations of different ethnic background and on the pathogenesis of ALCL could improve our understanding.

We observed a significantly worse outcome among adolescents with BL, as previously reported by other authors.^{17,18} In the NHL-BFM group, 5-year EFS was 88% in children compared to 82% in adolescents ($P = 0.06$).⁶ However, in a more recent study on pediatric patients with mature B lineage NHL, the 3-year EFS was 89% and 84%, for patients <15 years versus > 15 years of age, respectively.¹⁹ Differences in biology and genetics have been hypothesized to be responsible for this different outcome, but this question is still unanswered. Mbulaiteye *et al.* found that BL incidence may have trimodal incidence peaks, and concluded that BL peaking at different ages might have different etiology and/or biology.²⁰ Trautmann *et al.* reported age biased differences, with two gene rearrangements occurring almost exclusively in patients <14 years of age, and hypothesized that an antigen-driven selection might differ between pediatric and adult Burkitt's lymphoma cases.²¹ Other authors did not find significant differences between pediatric and adult BL with respect to immunophenotype, genomic aberrations or gene expression profiles.²²

Table 2

Late effect	Total patients	< 15 year old	15-18 year old
Neuro-cognitive	6	6	0
Neurological	3	3	0
GH deficiency	1	1	0
Hypothyroidism	1	0	0
Hypogonadism	4	3	1
Hypertension	1	0	0
Cardiac	2	2	0
Obesity	4	3	1
Diabetes insipidus	1	1	0
Osteoporosis	2	2	0
AVN	2	1	1
Kidney function	1	1	0
Bronchiolitis obliterans	1	1	0

The addition of rituximab to the therapy of all mature B-NHL, based on the results of the recently closed international study, has proven beneficial both in children and adolescents.²³ Our paper focuses on patients treated before the introduction of rituximab, to have a homogenous population, and therefore does not contribute information in this respect.

We observed a trend towards an inferior outcome for adolescents with LL. This has also been reported previously.²⁴⁻²⁶ Termuhlen *et al.*, reported that among patients with advanced stage LL, age <10 years was associated with improved outcomes ($P < 0.001$).²⁷ The CCG502 trial reported an increased relative risk of treatment failure of 2.7 for the 38 patients >14 years of age compared with 156 patients <10 years of age at diagnosis ($P = 0.008$).²⁸ Similar results were reported by the BFM.⁶

In this report, there was no difference in outcome related to age in ALCL, which is similar to the literature data.^{29-31,6} Although not significant, the finding of an increased incidence of ALK1-negative ALCL in the adolescent group is in keeping with other reports.³²⁻³⁴

Regarding outcomes, patients <15 years experienced more treatment-related complications but had slightly lower treatment-related mortality. The long-term toxicities including second malignancies were lower than expected,³⁵ explained by the combination of short follow up time in some patients and the use of newer treatment regimens designed to maintain survival while reducing long-term morbidity.

Our series presents some limitations. While the advantage of a single institutional series lies in the homogeneous radiological and pathological assessment, the limitation is in the small size of the study population. We decided to use the WHO 2001 classification, as using the 2008 revised version³⁶ would have led to further dividing into

subgroups too small to allow any statistical analysis. As well, being a pediatric tertiary care center, we provided all patients, including the teenagers, consistent care with pediatric protocols, maximum enrollment into clinical trials when available, thus eliminating some of the issues which have been associated with poor outcomes in adolescents (treatment in adult centers, poor compliance, poor enrolment into clinical trials). Thus the differences that we observed in outcome and toxicity are more likely to be related to real differences in the biology of the disease between children and adolescents.

Our results are similar to those reported by the large groups.^{3,6,23,24,28,37-46} The optimal treatment for adolescent NHL patients has not yet been established, and the reasons for the inferior outcomes in adolescents are not completely clear. Potential explanations include patient-related factors, disease-related factors and therapeutic strategies. Patient-related factors include psychosocial aspects unique to this age group, like the transition from the dependence of childhood to the autonomy of adulthood, including disagreements with authority figures, confusion about responsibilities, lack of communication, and failure to accurately perceive the severity of their cancer and the risk it poses. All of these factors will negatively affect the quality of cancer care they receive and their chances of survival.⁴⁷

In summary, we confirm the differences reported in the literature between children and adolescents (> 15 years at diagnosis), in particular with respect to better survival and reduced risk of long-term toxicity in children. While our population was homogeneously assessed and treated, differences were often non-statistically significant due to the low numbers. More collaborative research is needed to better define disease-specific age ranges, by analyzing disease-specific biology and patient characteristics.

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